Specialty Conference

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Inappropriate Secretion of Antidiuretic Hormone

DR. KELLER:* A 16-month-old white boy was admitted to hospital following one day of fever and obtundation. He was well until four days before admission when a nasal discharge and cough developed. On the day of admission a temperature of 104°F had been noted. He had become obtunded, crying only when touched. Consequently, he was seen at the United States Naval Hospital, San Diego, where a lumbar puncture was done. The spinal fluid contained 2,700 leukocytes per cu mm with 94 percent polymorphonuclear leukocytes and many Gram-negative coccobacilli.

The patient was transferred to University Hospital. On admission a temperature of 101°F was recorded, with a pulse rate of 140 and a respiratory rate of 44 per minute. Blood pressure was normal. The pertinent positive physical findings were pronounced nuchal rigidity; a dull, thickened right tympanic membrane; and a slight amount of clear rhinorrhea. The blood and cerebrospinal fluid cultures grew Hemophilus influenza.

Ampicillin was given parenterally at a dosage of 300 mg per kg of body weight every 24 hours. Fluids were given at a rate half that of his calculated maintenance requirements. The fever cleared on the second hospital day. On day one, oliguria developed. Tests of urine showed a specific gravity of 1.042 and an osmolality of 882 milliosmols (mOsm) per kg of H_2O. A test of serum osmolality done at the same time gave results of 270 mOsm per kg of H_2O. A diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) was made. The laboratory data are summarized in Table 1.

On day two, ethyl alcohol was given by mouth and the urine specific gravity fell to about 1.010. Fluid administration was decreased to a rate one-third that of the calculated maintenance fluid requirements and additional fluid was given to replace the volume of urine excreted. On day three, ethyl alcohol was again given but there was no increase in the volume of urine output. On day four, the patient began to show clinical improvement in his level of consciousness. Strict fluid restriction was continued and by day five urine osmolality and serum osmolality had become appropriate. The remainder of his hospital course was unremarkable.

DR. MENDOZA:† The syndrome of inappropriate antidiuretic hormone secretion is one which many consider a rare and esoteric problem. One of the points that I want to make is that, at least in a mild form, SIADH is a common problem in pediatrics. It occurs most frequently after meningitis and after surgical operation. In general, the syndrome is so mild that it causes no symptoms because patients at risk are routinely given a

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TABLE 1.—*Laboratory Data of the Patient Presented*

Day	Wt. kg	Fluid intake ml	Fluid output ml	U_{osm} mOsm/kg	P_{osm} H_2O	Serum[Na] mEq/L
1	8.9	380	70	..	..	..
2	8.9	435	115	882	270	136
3	9.0	335	100	421	269	136
4	9.1	405	280	535	..	132
5	8.9	630	513	58-257	257	..

U_{osm} and P_{osm} refer to the osmolality of the urine and serum, respectively.

TABLE 2.—*Criteria for the Diagnosis of SIADH*

1. No dehydration
2. Hyponatremia and hypoosmolality
3. Normal renal function
4. Normal adrenal function
5. Urine inappropriately concentrated
6. Urinary sodium excretion present

lower fluid intake than the usual maintenance fluids.

The best place to begin in discussing SIADH is with a short discussion of the renal concentrating mechanism, with an emphasis on what antidiuretic hormone (ADH) does and on the appropriate stimuli for ADH secretion. After the appropriate conditions for ADH secretion are clear, we can go on to discuss inappropriate ADH secretion.

In the nephron, filtration occurs at the glomerulus. Throughout the proximal tubule, there is active reabsorption of sodium. The proximal tubule is highly permeable to water so that when sodium is actively reabsorbed, water is passively reabsorbed. Therefore, the osmolality of proximal tubular fluid remains the same as that of plasma (approximately 300 mOsm per kg of H_2O). The tubular fluid then enters the loop of Henle, which passes through the medulla.

The medullary interstitium is hypertonic and has a high concentration of both sodium and urea. As the tubular fluid moves along the descending limb of the loop of Henle, water diffuses from the lumen along its osmotic gradient and at the same time sodium and urea diffuse into the lumen. The relative magnitude of solute influx and water efflux is controversial. Both mechanisms result in a tubular fluid that is increasingly hypertonic as it moves along the descending limb of the loop of Henle. The osmolality reaches about 1,200 mOsm per kg of H_2O at the so-called "hairpin turn."

The ascending limb of the loop of Henle is impermeable to water. Essentially no water leaves or enters the lumen, but the tubular fluid becomes diluted, because sodium chloride both diffuses and is actively transported from the ascending limb. By the time the tubular fluid reaches the early distal tubule, its osmolality is about 100 mOsm per kg of H_2O. The changes in tubular fluid osmolality which occurs before this point in the nephron occur whether the animal is in maximum water diuresis or in maximum antidiuresis. In other words, the tubular fluid is dilute in the early distal tubule even in the presence of a maximal concentration of circulating ADH.

The major effect of ADH is to increase the permeability to water of the distal tubule and collecting duct. As a result of the increased permeability, water diffuses from the tubular lumen and the osmolality of the tubular fluid becomes equal to that of the surrounding interstitial fluid. In the distal tubule and cortical collecting duct the tubular fluid becomes isotonic to plasma in the presence of ADH. As the tubular fluid passes through the medullary collecting duct, it becomes increasingly hypertonic as it is exposed to the increasingly hypertonic medullary interstitium. In maximum antidiuresis, the final urine osmolality is 1,200 to 1,400 mOsm per kg of H_2O. Thus, in the presence of ADH, the kidney reabsorbs water in the distal tubule and collecting duct. This water is reabsorbed largely in the absence of solute (free water is reabsorbed).

The two physiologic stimuli for the secretion of ADH are: (1) an increase in the osmolality of the extracellular fluid; and (2) a decrease in the extracellular fluid volume. These stimuli are logical teleologically. ADH causes increased water reabsorption, and the two situations in which water reabsorption is appropriate are hyperosmolality and volume depletion.

Table 2 gives criteria for the diagnosis of SIADH. First, there must be no dehydration. If the patient's extracellular fluid volume is diminished, he has ADH secretion but it is physiologically appropriate. Second, there must be a low serum sodium concentration and, therefore, a low serum osmolality. If the serum sodium concentration and the serum osmolality are high, ADH secretion is physiologically appropriate. Third, there must be normal function of the kidneys and of the adrenal glands. Dysfunction of either organ can cause abnormal salt and water metabolism and hypoosmolality independent of ADH. Fourth, the osmolality of the urine must be higher than is appropriate for the patient's condition. The urine does not have to be more concentrated than plasma in order to be inappropriate, since even a

dilute urine may be inappropriately concentrated.

Bartter and Schwartz[1] created a hypothetical case to illustrate this point. A normal person might ingest 400 mOsm and two liters of water daily in addition to his insensible water loss. He would excrete two liters of urine a day containing 200 mOsm per liter. At the end of the day, a total of 400 mOsm in two liters of water would be excreted, the urinary concentration would be low, and water and osmolar balance would be maintained. In the presence of a small excess of ADH secretion only 1,800 ml of urine a day might be excreted. The urinary osmolality would be 222 mOsm per kg of H_2O, which is hypotonic to serum, but 200 ml of free water would be retained. If this continued day after day, SIADH would result. The point of this example is that although most patients with SIADH have highly concentrated urine, as was true in the patient presented today, concentrated urine is not necessary to make the diagnosis of SIADH. What is necessary is that the urine be inappropriately concentrated for the physiologic setting. The final criterion for the diagnosis of SIADH is continued excretion of sodium in the urine. This aspect will be discussed in more detail later.

The classic description of the SIADH was made in 1957 by Schwartz et al[2] in patients with carcinoma of the lung, in particular, oat cell carcinoma of the lung. Since this original report, a number of workers have fractionated oat cell carcinomas and isolated a substance which is immunologically[3] and physiologically[4] identical to normal human antidiuretic hormone (arginine vasopressin). Although it is not definitely known whether this results from a trapping and concentration of circulating ADH in the tumor or from the synthesis of ADH by the tumor, most workers assume that the tumor is making the hormone. Since the original descriptions, ADH-like material has been described in several other tumors as well. These tumors are of little consequence to pediatricians, but we frequently see SIADH in children in disorders involving the central nervous system, particularly meningitis.[5] It is my feeling that essentially all children with meningitis have SIADH at least in a mild form. We generally assume that this is the case and restrict fluid intake during the course of acute meningitis. SIADH is also seen in a variety of other central nervous system disorders such as head injury, brain abscess and brain tumor. SIADH also occurs in a number of pulmonary conditions such as pneumonia or tuberculosis.

What are the signs and symptoms of SIADH? In many cases there are none. The existence of clinical findings in this condition indicates that the diagnosis has been delayed. All of the symptoms of SIADH occur because the patient has water intoxication. If the diagnosis is made early, and if the serum osmolality is kept above about 240 mOsm per kg of H_2O, the patient is likely to be asymptomatic. The only way the diagnosis can be made in such a patient is by laboratory tests. This was the case with the child presented this morning. Usually the syndrome progresses no further, but occasionally symptoms do develop. The mildest symptoms of SIADH are anorexia and nausea. As the syndrome becomes more severe, personality changes develop. These symptoms usually occur when the serum sodium falls to 110 to 120 milliequivalents (mEq) per liter. If the serum sodium falls below 110 mEq per liter, neurologic signs can occur such as decreased reflexes, pronounced weakness, Babinski reflexes, stupor and, finally, convulsions and death.

The values given here relating the serum sodium concentration with symptoms are not absolute. Occasionally patients have significant symptoms at serum sodium levels above 120 mEq per liter while other patients with serum concentrations in the 105 to 110 mEq per liter range may have slight lethargy without other symptoms. The apparent explanation for this is that the rate at which dilution occurs in the patient is also important. However, the relationship of serum sodium concentration to symptoms applies fairly well in the pediatric age group because children generally have acute SIADH. In contrast, adults with oat cell carcinomas have SIADH for as long as they survive their primary disease. The syndrome is significantly different in such patients who may become hypotonic over a relatively long period of time. They often tolerate a given degree of hypotonicity better than children with SIADH who have become hypotonic more quickly.

There is no way to prevent inappropriate secretion of ADH, but therapy can prevent or minimize symptoms. There are three major forms of therapy of SIADH. The most significant of these is fluid restriction. If fluid intake is restricted to less than insensible water loss, serum osmolality will slowly rise and symptoms, if present, will disappear. In fact, it is theoretically possible to give a patient with SIADH no fluids without danger.

The second approach to therapy is the administration of sodium chloride. This is not necessary,

however, unless the child is acutely symptomatic from his hyponatremia (which usually means he is having seizures). In such a situation, it is essential to increase the serum sodium concentration more rapidly than by fluid restriction alone. These patients should be given sufficient hypertonic sodium chloride to raise the serum sodium concentration about 10 mEq per liter (mEq NaCl to be infused = .63 × body wt in kg × 10 mEq). In symptomatic patients, the infusion of hypertonic sodium can be lifesaving. If the patient is hypotonic but has no significant symptoms, sodium chloride infusion is not indicated, since such patients will excrete any sodium load given. Continued loss of sodium in the urine is one of the hallmarks of SIADH.[6,7]

At first it was thought that the hyponatremia in SIADH was a result of dilution of body fluids by the retained water. However, very careful balance studies have been done in a number of patients, especially in adults with chronic SIADH, and serum osmolality falls more than can be explained on the basis of the amount of water retained. Another possible explanation for the hyponatremia is that there is a loss of sodium in the urine. Urinary sodium concentrations in patients with SIADH are inappropriately high. When the serum sodium concentration is low, it is appropriate to have a urine sodium concentration of nearly zero, with subsequent sodium retention and correction of the hyponatremia. Patients with SIADH have a relatively high urine sodium concentration. However, if the urinary sodium loss and the water retention are both considered, the hyponatremia is still not completely explained. The question of what happens to the sodium is unanswered. The popular explanation is to say that it becomes bound in a form that is osmotically inactive (another way of saying that the sodium disappears). What this actually indicates, however, is that we do not really know where the sodium goes.

When the patients are water restricted and recover from SIADH, they lose weight and retain sodium. The rise in serum sodium concentration with recovery also cannot be explained fully by water loss or sodium retention or both. Thus, the sodium seems to "reappear" with recovery. It is useless to treat an asymptomatic patient with SIADH by giving him salt because he will excrete the sodium load in the urine over the next 12 to 24 hours. The continued excretion of salt in patients with SIADH appears to be caused by depressed proximal tubular sodium reabsorption resulting from fluid retention and concomitant extracellular fluid volume expansion. The only indication for salt infusion is a convulsing or deeply stuporous child. In such a child, sodium should be infused and then serum sodium concentration maintained by fluid restriction.

The third form of therapy is alcohol, which was tried in the patient presented. The use of alcohol is interesting physiologically. The diuretic effects of alcohol are well recognized. Alcohol decreases the secretion of ADH from the pituitary gland. The administration of alcohol in moderate amounts inhibits ADH secretion and reverses the syndrome in many but not all children with SIADH. There is no explanation for the variability of its effect. In a number of children there may be a dramatic increase in urine output after the administration of alcohol. However, alcohol does not decrease tumor-produced ADH. Therefore, the administration of alcohol in a patient with SIADH may distinguish between production of ADH by an autonomous tumor or by the pituitary.

In summary, SIADH is not a rare, esoteric condition. We see it frequently in postoperative patients and in patients with meningitis. Its symptoms are often mild because we routinely restrict fluid intake in these patients. It is, however, a potentially life-threatening problem if allowed to progress untreated. On the other hand, if the diagnosis is made early, SIADH can be a completely benign condition.

DR. SCHULTZ:* I would like to support the contention that inappropriate ADH response is quite common in meningitis and probably is the rule rather than the exception. Very likely the most common cause of inappropriate ADH seen in many hospitals is something other than meningitis, namely pneumoencephalography. A controlled series, studying pneumoencephalograms done for various conditions, showed that over half of the patients develop SIADH.

It is interesting that one may feel bad that the child lost cerebrospinal fluid and in order to replenish it one writes the almost routine orders following pneumoencephalographic studies, "Keep flat on back, force fluids." If the nurses really force fluids, this is forcing water on a child with SIADH. We wonder why some of these patients do not wake up quickly after pneumoencephalography and why they do not feel well the

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next day. I am sure this contributes to the morbidity of the procedure.

QUESTION FROM THE AUDIENCE: *What is the dose of alcohol and what are some of the other symptoms from it?*

DR. MENDOZA: The best studies on the effect of alcohol as an inhibitor of ADH secretion were done in adults in the 1940's. These volunteers were given four ounces of bourbon. I've extrapolated from that to get a dose of 1 ml of alcohol per kg of body weight, given mixed in orange juice. I've never seen anybody develop other symptoms from that dose.

QUESTION FROM THE AUDIENCE: *Is there any abnormality in aldosterone metabolism in* SIADH?

DR. MENDOZA: The answer is probably yes. It is a fact that aldosterone levels are low or low to normal in patients with SIADH, which could contribute to the hyponatremia and sodium loss. The importance of this in the overall pathogenesis of SIADH is unclear. The sequestering of sodium and the sodium loss in the urine can both be prevented by decreasing the fluid intake. That is, if a patient has an oat cell carcinoma and SIADH and is given water, the serum will become hypotonic. The patient will retain water, decrease proximal tubular sodium reabsorption and hide that sodium which mysteriously becomes osmotically inactive. All this can be prevented by preventing excess water intake. The aldosterone deficiency may be insignificant in the pathogenesis of the syndrome, since the aldosterone levels do not change with water restriction which prevents sodium loss.

QUESTION FROM THE AUDIENCE: *Could the sodium be in the cells?*

DR. MENDOZA: The fact is that the intracellular total cation concentration has to be quite low since intracellular osmolality always equals extracellular osmolality in the steady state. Various investigators have measured the loss not only of sodium but of potassium, calcium, magnesium, and other cations. However, it is still not possible to explain the hypoosmolality on the basis of cation loss. Therefore, there must be some cation that is unavailable to total body water in terms of its osmotic activity.

QUESTION FROM THE AUDIENCE: *Does alcohol change the sodium excretion?*

DR. MENDOZA: It does secondarily because if therapy with alcohol is successful, there is water diuresis and the normal plasma volume and total body water return. As I mentioned, when there is normal plasma volume and total body water there is no excessive salt loss in spite of the continuation of inappropriate ADH secretion. This can be shown both in patients with oat cell carcinoma and in experimental animals or human volunteers given repeated injections of vasopressin.

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